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## PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 07005/003WO2	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US98/15563	International filing date (day/month/year) 28 JULY 1998	Priority date (day/month/year) 29 JULY 1997
International Patent Classification (IPC) or national classification and IPC IPC(6): A61K 38/10, 39/00; C07K 7/06, 7/08 and US Cl.: 424/184.1; 514/2, 14; 530/327		
Applicant THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND		

<ol style="list-style-type: none"> <li>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</li> <li>2. This REPORT consists of a total of <u>4</u> sheets.</li> </ol> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>0</u> sheets.</p>
<ol style="list-style-type: none"> <li>3. This report contains indications relating to the following items:           <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step or industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input type="checkbox"/> Certain documents cited</li> <li>VII <input type="checkbox"/> Certain defects in the international application</li> <li>VIII <input type="checkbox"/> Certain observations on the international application</li> </ul> </li> </ol>

Date of submission of the demand 13 JANUARY 1999	Date of completion of this report 16 NOVEMBER 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized office MARIANNE DIBRINO Telephone No. (703) 308-0196
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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/15563

## I Basis of the report

1. This report has been drawn on the basis of (Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):

the international application as originally filed.

the description, pages 1-62, as originally filed.

pages NONE, filed with the demand.

pages NONE, filed with the letter of \_\_\_\_\_.

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

the claims, Nos. 1-57, as originally filed.

Nos. NONE, as amended under Article 19.

Nos. NONE, filed with the demand.

Nos. NONE, filed with the letter of \_\_\_\_\_.

Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

the drawings, sheets/fig NONE, as originally filed.

sheets/fig 1-16, filed with the demand.

sheets/fig NONE, filed with the letter of \_\_\_\_\_.

sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

the description, pages NONE.

the claims, Nos. NONE.

the drawings, sheets/fig NONE.

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the **Supplemental Box** Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>(Please See supplemental sheet)</u>	YES
	Claims <u>(Please See supplemental sheet)</u>	NO
Inventive Step (IS)	Claims <u>(Please See supplemental sheet)</u>	YES
	Claims <u>(Please See supplemental sheet)</u>	NO
Industrial Applicability (IA)	Claims <u>(Please See supplemental sheet)</u>	YES
	Claims <u>(Please See supplemental sheet)</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1, 4-7, 9-15, 18-24, 45-55 and 56 lack novelty under PCT Article 33(2) as being anticipated by Abrams *et al.* Abrams *et al.* teach a method for stimulating an immune response specific toward a naturally occurring protein in an animal having an immune system including T cells, said method comprising administering to said animal an altered protein derived from said naturally occurring protein, wherein an unstable polypeptide segment has been inserted by artifice into said altered protein and wherein said naturally occurring protein is from a neoplastic cell. Abrams *et al.* teach the method wherein the altered protein comprises a T cell epitope which has properties in common with the instant invention. Abrams *et al.* teach a method for detecting T cell epitopes which comprise at least twelve amino acid residues (Tables 3 and 4 and Figure 1).

Claims 39-44 and 57 lack novelty under PCT Article 33(2) as being anticipated by Evavold *et al.* Evavold *et al.* teach that altered peptides have affected the induction and severity of disease in experimental autoimmune encephalomyelitis and adjuvant arthritis models of autoimmunity.

Claims 1-3, 7, 15-17, lack an inventive step under PCT Article 33(3) as being obvious over Martin *et al.* in view of Schulz *et al.* Martin *et al.* teach selective activation of different effector functions of CD8+ T lymphocytes by altered peptide ligands wherein the T cell epitopes are from the glycoprotein of lymphocytic choriomeningitis virus. Schulz *et al.* teach that different epitopes of the viral glycoprotein are being recognized by T cells of different haplotypes and that the alterations in the peptides comprising the T cell epitopes affected CTL upregulation. Martin *et al.* and Schulz *et al.* do not teach administering altered peptides to an animal or to a human patient. However, *in vitro* activity is well known and well utilized as an indicator of *in vivo* effects. Therefore, it would have been obvious for a person of ordinary skill at the time the invention was made to be motivated to practice the methods of Martin *et al.* and Schulz *et al.* *in vivo* in mammalian models. Therefore, the invention as a whole was *prima facie* obvious to (Continued on Supplemental Sheet.)

## Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

## V. 1. REASONED STATEMENTS:

The report as to Novelty was positive (YES) with respect to claims 2, 3, 8, 16, 17, 25-38, 51-54.  
The report as to Novelty was negative (NO) with respect to claims 1, 4-7, 9-15, 18-24, 39-50, 55-57.  
The report as to Inventive Step was positive (YES) with respect to claims NONE.  
The report as to Inventive Step was negative (NO) with respect to claims 1-57.  
The report as to Industrial Applicability was positive (YES) with respect to claims 1-57.  
The report as to Industrial Applicability was negative (NO) with respect to claims NONE.

## V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1, 4-7, and 8 lack an inventive step under PCT Article 33(3) as being obvious over Abrams *et al.* Abrams *et al.* do not teach administering altered peptides to a human patient. However, murine models are used in biomedical research as surrogates for human disease. The goal of the therapeutic intervention is to treat human patients. Therefore, it would have been obvious for a person of ordinary skill at the time the invention was made to be motivated to practice the methods of Abrams *et al.* in humans. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 20, 25-39, and 41-44 lack an inventive step under PCT Article 33(3) as being obvious over Tiarks *et al.* Tiarks *et al.* teach decreasing potency of helper T cell-recognized epitopes in Factor VIII in patients receiving FVIII infusions. Tiarks *et al.* teach methods of detecting a polypeptide segment that is likely to be a T cell epitope. Tiarks *et al.* do not teach decreasing potency of helper T cell-recognized epitopes in allergy patients. However, the steps involved in altering the immunogen Factor VIII would be the same as altering an allergen. Therefore, it would have been obvious for a person of ordinary skill at the time the invention was made to be motivated to practice the methods of Tiarks *et al.* to modify allergens. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1-54 meet the criteria for PCT Article 33(4).

NEW CITATIONS

EVAVOLD *et al.* Tickling the TCR: Selective T-Cell Functions Stimulated by Altered Peptide Ligands. *Immunology Today*. December 1993, Vol. 14, No. 12, pages 602-609, see entire document.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/15563

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/10, 39/00; C07K 7/06, 7/08  
US CL :424/184.1; 514/2, 14; 530/327

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 424/184.1; 514/2, 14; 530/327

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
MEDLINE, BIOSIS, CAPLUS, WPIDS, APS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MIKSZTA ET AL. Conversion of Low Antibody Responders into High Responders by Up-regulating the T Cell Response to a Selective Epitope. J. Immunol. October 1996, Vol. 157, No. 7, pages 2883-2890, see entire document.	1-57
Y	MARTIN ET AL. Selective Activation of CD8 T Cell Effector Functions by Epitope Variants of Lymphocytic Choriomeningitis Virus Glycoprotein. J. Immunol. September 1996, Vol. 157, No. 6, pages 2358-2365, see entire document.	1-57
Y	ABRAMS ET AL. Mutant ras Epitopes as Targets for Cancer Vaccines. Seminars in Oncology. February 1996, Vol. 23, No. 1, Pages 118-134, see entire document.	1-57

Further documents are listed in the continuation of Box C.  See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"a."	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

01 OCTOBER 1998

Date of mailing of the international search report

22 October 1998

Name and mailing address of the ISA/US  
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/15563

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6: A61K 38/10-39/00; C07K 7/06, 7/08

US CL: 424/184-1; 514/2, 14; 530/327

According to international Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

US: 424/184-1; 514/2, 14; 530/327

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, CAPLUS, WPIDS, APS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MIKSZTA ET AL. Conversion of Low Antibody Responders into High Responders by Up-regulating the T Cell Response to a Selective Epitope. J. Immunol. October 1996, Vol. 157, No. 7, pages 2883-2890, see entire document.	1-57
Y	MARTIN ET AL. Selective Activation of CD8 T Cell Effector Functions by Epitope Variants of Lymphocytic Choriomeningitis Virus Glycoprotein. J. Immunol. September 1996, Vol. 157, No. 6, pages 2358-2365, see entire document.	1-57
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"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"
"O"	document referring to an oral disclosure, use, exhibition or other means	"A"
"P"	document published prior to the international filing date but later than the priority date claimed	document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
		document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
		document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
		document member of the same patent family

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/15563

## C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages.	Relevant to claim No.
Y	DIARKS ET AL. Hypothesis for the Control of Clotting Factor VIII Inhibitory Antibodies by Decreasing Potency of Helper T Cell-Recognized Epitopes in Factor VIII. <i>Scand. J. Immunol.</i> November 1992, Vol. 36, No. 5, pages 653-660, see entire document.	1-57
Y	SCHULZ ET AL. Major Histocompatibility Complex Binding and T Cell Recognition of a Viral Nonapeptide Containing a Minimal Tetrapeptide. <i>Eur. J. Immunol.</i> May 1991, Vol. 21, No. 5, pages 1181-1185, see entire document.	1-57
Y	SUN ET AL. Interleukin-2-Secreting Mouse Fibroblasts Transfected with Genomic DNA from Murine Neoplasms Induce Tumor-Specific Immune Responses That Prolong the Lives of Tumor-Bearing Mice. <i>Cancer Gene Therapy</i> September 1995, Vol. 2, No. 3, pages 183-190, see entire document.	1-57

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